VI. HEALTH EFFECTS IN HUMANS

Introduction

Data on the human health effects observed following exposure to chloramines are limited to a few clinical reports and epidemiologic studies. Several cases have been reported where chloramine-T has caused allergic contact dermatitis. Clinical reports indicate that acute chloramine exposure either by inhalation or ingestion results in burning eyes and throat, dyspnea, coughing, nausea, reversible pulmonary damage and allergic responses. One epidemiologic study looked at a population exposed to chloramine in its drinking water and used the disease risk as a baseline for comparing the risk in a population exposed to chlorine in its drinking water. These findings will be addressed only briefly as they are not directly relevant to this document. Damage to red blood cells has been observed in high risk subpopulations such as hemodialyzed individuals.

Clinical Reports and Experiments

Lombardi et al. (1989) reported the work related case of a 38-year-old nurse who developed subacute eczema that appeared to be caused by the use of chloramine-T as an antiseptic disinfectant in the cleansing of burns. Only a few cases of sensitization to chloramine-T have been reported and usually from nonoccupational contact even though it has widespread use in Italy as an antiseptic, disinfectant and chemical reagent.

Laakso et al. (1982) reported the case of a 27-year-old woman who mixed ~500 mL of 4-5% household ammonia with the same amount of 5% sodium hypochlorite bleach in a small, poorly ventilated bathroom. The vapors from the mixture caused burning in the eyes and throat, dyspnea, coughing, nausea and vomiting. Inhalation of the chloramine fumes resulted in pneumonitis, which did not result in permanent pulmonary damage.

Beck (1983) reported the case of a 28-year-old nurse who suffered from rhinitis when she was in contact with a chloramine solution. Chloramine is often used as an antiseptic in the treatment of infected ulcers, and when the nurse was treated with a 2% chloramine solution for a dental abscess, a severe angioneurotic edema developed. Since this Type I reaction to chloramine was reported only once before, the authors recommended that a prick test with chloramine be used before treatment of patients with previous exposures.

A clinical study was conducted by Lubbers et al. (1981) to assess the safety of chronically administered chlorine water disinfectants in humans. This study was conducted in three parts over a 12-week period. Phase I and Phase II subjects were male college students between the ages of 21 and 35 years of age, of normal body weight and free of any history of disease or any medical or surgical condition that might interfere with the absorption, excretion or metabolism of substances by the body. Phase III subjects were glucose-6-phosphate dehydrogenase deficient, but were normal in all other respects.

Phase I consisted of an increasing dose tolerance analysis in which progressive doses of chlorine were administered in water as chlorate, chlorine dioxide, chlorite, chlorine and chloramine to six groups, 10 subjects/compound with 10 subjects in the control group that received untreated water. Chloramine was given every 3 days for a total of 15 days, at concentrations of 0.01, 1.0, 8.0, 18.0 and 24.0 mg/L (corresponding doses of 0.14, 14, 110, 260 and 340 ug/kg/day assuming a body weight of 70 kg) in a total volume of 1000 mL.

Phase II consisted of 60 subjects randomly assigned into six treatment groups of 10 subjects/group with one group receiving untreated water. A daily concentration of 5 mg/L chloramines in a volume of 500 mL of water was administered for 12 consecutive weeks. Physicals and collection of blood and urine were conducted on a weekly basis during the treatment period and for 8 weeks following.

Phase III was conducted on male students who were deficient in glucose-6-phosphate dehydrogenase and were considered to be more susceptible to oxidative stress. These students were given 5 mg/L of sodium chlorite daily in a volume of 500 mL for 12 consecutive weeks.

Blood and urine samples were collected and physical exams were given, including blood pressure measurements and taste tests. During all three phases of this study a massive volume of raw data was acquired. No definitive finding of detrimental physiologic impact was made in any of the three phases of this human investigation of

the relative safety and tolerance of oral chlorine disinfectant ingestion. Other possible confounders such as diet and other sources of drinking water were not addressed. The fact that there were no overt adverse health effects within the limitations of this study suggests that ingestion of chloramine at these levels over a relatively short period of time produces no toxicity in healthy adult males, but does not rule out the possibility that longer treatment periods would result in any detectable adverse outcomes of biologic significance.

Epidemiology Studies

There are no epidemiologic studies that have been designed to address specifically the potential adverse effects of exposure to chloramines on human health. The study of Zierler et al. (1986, 1988) was designed in response to earlier ecologic studies that indicated that areas using chlorinated surface waters for drinking water were associated with higher cancer mortality than areas using other sources of drinking water and disinfectant practices. The addition of chlorine to surface water is known to form organic micropollutants (Murphy and Craun, 1990). Specifically, the reaction of free chlorine with naturally occurring precursor substances, primarily humic and fulvic acids, produces a group of halogen-substituted single-carbon compounds known as trihalomethanes (THMs) (Craun, 1988). The predominant THMs formed are chloroform and bromodichloromethane. The process of chloramination produces only small amounts of THMs. It was originally thought that the early findings of increased cancer mortality associated with chlorinated drinking water might be due to exposure to the THMs themselves. Zierler's study in Massachusetts was conducted to see if there was

a difference in cancer mortality among communities using chlorine compared with communities using chloramine for disinfection. In this sense, the persons who were exposed to chloraminated drinking water were used as controls with the assumption being they would be much less exposed to chlorination by-products.

The first phase of this study (Zierler et al., 1986) looked at the patterns of cancer mortality among 43 communities using either chlorine or chloramine since 1938. All resident Massachusetts deaths among those 45 years and older and occurring during 1969-1983 were eligible for the study. Deaths were selected for inclusion if the last residence listed on the death certificate was in a community using chlorine or chloramine for disinfection. Cancers of the bladder, colon, kidney, pancreas, rectum, stomach, lung and female breast were thought to be related to chlorinated by-products of disinfection and were therefore treated as cases for a mortality odds ratio (MOR) analysis. Deaths from cardiovascular and cerebravascular disease, chronic obstructive lung disease and lymphatic cancer (N=214,988), considered to be unrelated to chlorinated by-products, were used for comparison. In general, cancer mortality was not associated with type of disinfectant in the MOR analysis. There was a slight association (MOR=1.05) for chlorine use noted only with bladder cancer that increased slightly (MOR=1.15, 95% confidence interval = 1.06-1.26) when lung cancer deaths were used for controls. Standardized mortality ratio analysis of the data set were generally unremarkable. There was a small increase in mortality (SMR=118, 95% confidence interval = 116-120) from influenza and pneumonia in the chloraminated communities.

The second phase of this mortality study (Zierler et al., 1988) was designed to further pursue the bladder cancer findings in a more refined case-control analysis, which included decedent next-of-kin interviews. Information on cigarette smoking, occupation and residential history was obtained. The relationship with bladder cancer and residence in communities using chlorine for disinfection again persisted. The crude association was highest for lifetime residents of chlorinated drinking water communities relative to lifetime residents of chloraminated drinking water communities (MOR=1.5, 95% confidence interval = 1.1-2.2) when lymphatic cancers were used for controls. The MOR increased to 2.7 after controlling for the joint effects of age, gender, occupation and pack-years of cigarette smoking. Although the exposure estimates in these analyses are relatively crude, there is a consistent relationship, albeit small, with bladder cancer mortality and years of exposure to chlorinated drinking water when compared with years of exposure to chloraminated drinking water. The study was not designed to assess adverse effects from exposure to chloramine, but rather considers the chloramine-exposed participants as controls. At this time there are no epidemiologic studies that have evaluated chloraminated drinking water as the exposure of interest and not the control exposure.

High-Risk Subpopulations

Eaton et al. (1973) studied hemodialyzed patients (number of subjects not reported) from three University of Minnesota hospitals. They observed significant methemoglobinemia (>5% statistical analysis not provided) and Heinz body inclusions in the red cells of the patients in two hospitals, which used unpurified tap water and

water purified with the reverse osmosis (RO) technique during dialysis. The RO technique removes particulate matter and trace metals from the dialysis water. Charcoal-filtered RO water that did not contain chloramines was used in the third hospital, and did not result in significant methemoglobinemia. Serial observation of several patients exposed to chloramines through dialysis suggested that the RBC oxidant damage was cumulative. In addition to oxidant damage to the RBC, chloramines inhibit the metabolic pathway used by these cells to prevent and repair such damage. Thus, chloramine-containing dialysis water presented a severe threat of acute hemolytic anemia to uremic patients undergoing dialysis.

Kjellstrand et al. (1974) also observed similar effects in patients undergoing hemodialysis. The authors concluded that chloramines induced their deleterious effects through the formation of methemoglobin from the direct oxidation of hemoglobin, and through damage of the hexosemonophosphate shunt (HMPS), with which red cells defend themselves against oxidant damage. The authors suggested that chloramine-induced hemolysis may be reduced by the addition of ascorbic acid to the treatment water.

Summary and Discussion

Few acute exposures to chloramines have been reported in the literature. Laakso et al. (1982) reported pneumonitis as a result of inhalation of chloramine fumes from a mixture of household ammonia and sodium hypochlorite. Permanent pulmonary damage

was not sustained. Beck (1983) reported a Type I allergic response after treatment with a 2% chloramine solution for a dental abscess.

One experimental study on chloramines was located in the available literature. Lubbers et al. (1981) reported no hematologic or abnormal effects following routine clinical tests in individuals ingesting 0.01, 1.0, 8.0, 18.0 and 24.0 mg/L (0.14, 14, 110, 260 and 340 mg/kg/day, respectively) chloramines for 1 day in drinking water or 5 mg/L chloramines for 12 weeks in drinking water. It is unknown, however, whether exposure beyond this time would have any impact.

Although mentioned here for the sake of completeness, the work of Zierler et al. (1986, 1988) should not be used as definitive evidence that chloramine exposure is not associated with adverse health effects in humans. Although statistically stable because they are based on large numbers of deaths, the community based SMR analyses represent a relatively crude means of assessing the relationship of a specific cause of death with a specific drinking water disinfection practice. If there is a positive relationship between these variables, it may go undetected because of the attenuating effects of random misclassification of the observed deaths into exposure categories. The case-control study of bladder cancer was designed to use the chloramine exposure as the comparison group and does not address the potential adverse effects from chloramine, although often misinterpreted in this way.

Hemodialyzed patients are a high-risk subpopulation for chloramine exposure through chloraminated dialysis water. Chloramines cause oxidant damage to red blood cells and inhibition of the hexose-monophosphate shunt with which red blood cells defend themselves against oxidant damage (Eaton et al., 1973; Kjellstrand et al., 1974). Thus, this high-risk group must also be considered when using monochloramine for disinfection of water used in dialysis.